REMARKS

Claims 7-13 and 25-45 are pending in the instant application. Claims 7-12 have been withdrawn and claim 14 has been canceled.

Claims 30 and 31 have been amended to address an improper dependency; the order of the claims has been switched and the dependency corrected; however no other substantive change to these claims has been made.

Claim 13 has been amended to include a promoter in the claimed vector. Support for this amendment may be found throughout the specification, for example, pages 7, 8-17, and in the Figures and Description of the Figures.

Claims 25 and 28 have been amended to correct the order in which the various elements should be present 5' to 3' on the vector. Support for these amendments may be found in Figure 18 and throughout the application, as discussed further below.

Claims 21 and 38 have been amended to recite "said first and second selection genes" rather than "the two selection genes" to reflect the antecedent basis for this limitation.

Support for the amendments to the claims may be found throughout the specification, including the originally filed claims. *No new matter has been added.* Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants thank the Examiner for removing several of the rejections from the prior Office Action and for entering the amendments to the claims and specification.

Drawings

The Examiner has indicated that "the drawings filed on 11/13/00 have been objected [to]. Applicants are requested to see the PTO 948 attached to the previous office action mailed on 6/4/02."

Applicants have concurrently submitted herewith formal drawings.

Claim Objections

The Examiner has objected to claim 30 because it improperly depends from claim 31. The Applicants have amended claims 30 and 31 to correct this dependency. Removal of the present objection is respectfully requested.

Rejection of Claims 25-37 Under 35 U.S.C. §112, 1st Paragraph (New Matter)

The Examiner has rejected claims 25-37 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "this is a new matter rejection." In particular, the Examiner is of the opinion that the newly claimed limitation "an expression vector comprising from 5' to 3' . . ." in claims 25-37 has no clear support in the specification. The Examiner has requested that Applicants present a detailed analysis as to why the claimed subject matter has clear support in the specification.

Applicants have amended claims 25 and 28 to recite an order of vector components as described in Figure 18 and throughout the specification, thus rendering this rejection moot. Support for the amendments is as follows. Specifically, Figures 18 A through G depict a variety of exemplary constructs that are within the scope of the instantly claimed invention. Although Figure 18 does not indicate the location of the 5' end, it is well known in the art that the promoter is generally upstream (i.e., toward the 5' end) of the genes which it controls, and thus Figures 18

A and B show a construct having a 3' to 5' orientation. The specification provides at page 15, lines 7 through 11 (emphasis added), that "[t]he diptheria toxin/HBEGF system . . . *can be configured in a number of different ways, some* of which are shown in the figures. As for all the constructs outlined herein, the use of additional components (labels including detection and selection labels), IRES sites, protease cleavage sites such as 2a and others, etc., can all be used." In Figures 18 C through G, although no promoter is indicated, it is generally understood by one of skill in the art that the promoter would be upstream of the genes which it controls, e.g., toward the 5' end, and in these Figures it is clear from the specification (which, as Examiner points out, requires that the promoter be operably linked to HBEGF) that the promoter would be present upstream from HBEGF. Figures 18 C through G thus depict the exemplary constructs going from 5' to 3', with a promoter present between the 5' end and HBEGF. It would thus be readily apparent to one skilled in the art that the presently claimed constructs could be constructed from the variety of disclosed components such as promoters, IRES sites, etc. disclosed on pages 6-15 in the application and in the Figures.

Applicants therefore respectfully submit that clear support for an expression vector comprising from 5' to 3' a promoter of interest, HBEGF, a 2a site, nucleic acid encoding GFP and an IRES site, may be found in the specification and Figures. Accordingly, claims 25-37 as amended, comply with the written description requirement, and Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 13 and 15-45 Under 35 U.S.C. §112, 1st Paragraph (Written Description)

The Examiner has rejected claims 13 and 15-45 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner is of the opinion that "with the exception of expression vectors comprising HBEGF linked to IL-4 ε

promoter, the skilled artisan cannot envision the detailed expression vector structure of the vectors" of claims 13 and 15-45.

Applicants respectfully submit that the present amendment of claims 13, 25 and 28 renders this rejection moot, as these amendments now require that a promoter be present in each of the claimed vectors.

The Examiner has further alleged that claims 13, 15-24, and 34-45, drawn to expression vectors comprising HBEGF and a second marker, are not disclosed in the specification. Applicants respectfully draw the Examiner's attention to the following examples. On page 9, lines 6-24, it is disclosed that a reporter or marker gene may be a death gene. On page 10, lines 1-9, it is further disclosed that the death gene reporter may be hooked up to a detection gene such as GFP or BFP, etc. Further, on page 13, line 6 through page 15, line 30, multiple embodiments with two or more reporter genes are disclosed. Still further, on page 15, lines 20-30 it is disclosed that "[T]hese constructs comprising the HBEGF gene can by fused as outlined herein *to any number of detectable or selectable genes as outlined herein* for other constructs, including green fluorescent protein(GFP) and all its derivatives...."

Claims 25 and 28 have been amended as described above, and are clearly described in by Figure 18 and in the specification.

Based on the above, Applicants submit that the specification clearly describes the vectors of the invention as set forth in claims 13 and 15-45. Thus, the instant specification satisfies the written description requirement for the claimed invention and Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 21 and 38 Under 35 U.S.C. §112, 2nd Paragraph

The Examiner has rejected claims 21 and 38 as having insufficient antecedent basis because they recite the limitation "said first and second selection genes" in line 4 but recite "the two selection genes" in line 5. Applicants have amended claims 21 and 38 to state "said first and second selection genes" in line 5. Applicants thus respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 13, 15, 16, 17, 19, 20, 30, and 32 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 13, 15, 16, 17, 19, 20, 30, and 32 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,613,563 Bl (Sosnowski *et al*) and U.S. Patent 6,465,253 (Wickham, *et al.*). In particular, the Examiner is of the opinion that

> [t]he claimed invention differs from the prior art teachings by reciting that the expression vector comprises IRES site. Wickham et al teach adenoviral vectors comprising HB-EGF, 2a site and GFP. Wickham el al do not teach that the vectors comprise IRES site. However, Sosnowski et al teach viral vectors with modified tropism. The reference teaches that the targeting ligand can be . . . (HBEGF) . . . The reference teaches that the DNA sequence of the ligand is generally introduced into a plasmid in operative linkage with an appropriate promoter (refers to the promoter of interest of the instant claims (e.g., see column 46). The reference teaches that elements that increase the expression of the desired product are incorporated into the construct, and such elements include internal ribosome binding site (IRES of the instant claims) (e.g., see column 49). Thus, it would have been obvious to one skilled in the art at the time the invention was made to use IRES site in the expression vectors such that the expression of the desired product is increased.

Applicants respectfully traverse the foregoing rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been

motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. 2143).

Even if a combination of prior art references teaches or suggests all of the claim limitations, no *prima facie* case of obviousness may be established without a motivation to combine. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *Id.* The level of skill in the art cannot be relied upon to provide the motivation to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

The Examiner has not set forth any motivation to combine these references and hence has not established a *prima facie* case of obviousness. Moreover, even if there were motivation to combine the references, the combination does not teach or suggest each and every element of the claims. U.S. Patent No. 6,465,253 teaches vectors comprising a nucleic acid molecule encoding

a chimeric protein comprising a "nonnative amino acid sequence," (a UTV sequence) which allows the protein to bind and enter cells more efficiently. An example of a UTV sequence is a 21 amino acid portion of HBEGF. Further, U.S. Patent No. 6,465,253 discloses that instead of a therapeutic gene, the vectors may be used to transfer a marker gene such as GFP. U.S. Patent No. 6,465,253 teaches that a protease recognition site may be present in the vectors, but does not specifically disclose that it is, or suggest it should be, a 2a site. Further, U.S. Patent No. 6,465,253 fails to teach or suggest the use of an IRES sequence in the vectors described therein which encode UTV sequences.

U.S. Patent No. 6,613,563 does not cure this deficiency. U.S. Patent No. 6,613,563 describes gene therapy vectors that are viral constructs which have their native tropism modified or ablated. In one embodiment, the tropism of a virus is modified by using a ligand to re-target the vector. Examples of ligands disclosed include FGF proteins and HBEGF. U.S. Patent No. 6,613,563 does not suggest that a 2a site be used. While U.S. Patent No. 6,613,563 mentions the use of a vector including an IRES site to increase the expression of the therapeutic gene incorporated in the tropism-modified vector, there is no teaching or suggestion that it should be used in any other type of vector, for example, the vectors of U.S. Patent No. 6,465,253. Further, as the design of gene expression vectors for gene therapy is an unpredictable art that is not always successful (as noted in the Backgrounds of both U.S. Patent Nos. 6,465,253 and 6,613,563), one would not have had a reasonable motivation to use or expectation of success in using the IRES of the vectors disclosed in U.S. Patent No. 6,613,563 in the vectors of U.S. Patent No. 6,465,253.

As set forth above, U.S. Patent Nos. 6,465,253 and 6,613,563 when combined fail to teach or suggest each and every limitation of the claims. Moreover, as stated above, there would have been no motivation for one of skill in the art to use the IRES of the tropism-modified vector

taught in 6,613,563 in any other type of vector. Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000

Respectfully submitted,

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